The incidence and severity of Clostridium difficile infection (CDI) is rising, primarily due to a new and virulent strain. The impact of CDI on patients with inflammatory bowel disease (IBD) should not go unrecognized since this is a high risk patient population. Unlike patients in the general population, those with IBD who acquire C. difficile tend to be younger, have less antibiotic exposure and have more community-acquired infections. The clinical presentation of CDI in IBD is also unique compared to the general population. Given the high burden of CDI in IBD patients who have an acute IBD flare, all patients should be tested for CDI. Treatment of CDI focuses on antibiotics, however, in IBD patients, attention is required regarding immunosuppression during treatment. The aim of this paper is to review the most updated information on CDI in IBD including the epidemiology, pathogenesis, clinical presentation, risk factors, diagnosis and treatment guidelines.

INTRODUCTION

Clostridium difficile (C. difficile) is an obligate, anaerobic, gram-positive, spore-forming bacillus that is associated with pseudomembranous colitis and the clinical spectrum ranges from asymptomatic carriage to severe colitis, sepsis and death.¹ In the United States (US), it is becoming an increasing health concern as its incidence is on the rise. C. difficile recently surpassed methicillin resistant Staphylococcus aureus (MRSA) as the most common hospital acquired infection in the US.² In addition, in 2014, deaths from CDI were greater than those associated with HIV infection.³ CDI is higher amongst females, whites and the elderly; however, CDI in IBD patients is also increasing.⁴,⁵

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In IBD patients, CDI may be more prevalent in ulcerative colitis (UC) than Crohn’s disease (CD).\(^6\) Patients with IBD complicated by CDI have higher mortality and resource utilization, including increased hospitalization, longer length of stay and higher inpatient morbidity.\(^7 - 10\) In addition, CDI complicating IBD may lead to an increase in the need for surgical intervention.\(^8\) Thus, it is important to evaluate CDI and its role in the IBD community.

**Epidemiology of CDI**

CDI is a major cause of morbidity and mortality worldwide and in the US in particular. In 1978, *C. difficile* was first recognized as a major cause of antibiotic related colitis. Since then the incidence and severity of CDI has increased with a particular rise in the past decade. From 2000 to 2006, the number of hospitalizations secondary to CDI nearly doubled in the general population in the US, with a reported annual incidence of 300,000 hospitalizations and an annual healthcare cost of 4.8 billion dollars.\(^11,12\) In 2011, there were over 450,000 cases of CDI, resulting in approximately 30,000 deaths.\(^13\) The incidence of hospitalizations, however, minimizes the true prevalence of CDI, as community acquired infections are also on the rise and account for nearly 27% of all *C. difficile* related infections.\(^14\)

The emergence of a highly virulent *C. difficile* strain (B1/NAP1/027) serves as a predictor of disease severity and risk of mortality.\(^15\) This strain, which is group B1 (restriction-endonuclease analysis), type NAP1 (North American PFGE type 1) and ribotype 027 (polymerase chain reaction), is resistant to fluoroquinolones and has been shown to produce larger amounts of toxin than other *C. difficile* strains.\(^14,16\) This is due to a mutation of the regulatory *tcdC* gene and the production of *C. difficile* transferase, an ADP-ribosylating binary toxin.\(^17\) One in vivo study compared a reference *C. difficile* strain in mice to the B1/NAP1/027 strain and found that the B1/NAP1/027 strain has at least 11 different antigenic epitopes compared to the reference strain, with less susceptibility to antibody neutralizations. Furthermore, it exhibits a lower dose needed for virulence compared to the reference strain.\(^18\)

Patients with IBD have an increased risk and higher incidence of CDI compared to the general population.\(^5,19\) In a retrospective analysis of nationwide inpatient admissions for CDI in those with IBD, CDI prevalence in the general population had an incidence of 4.5 per 1000. CDI was higher among those with UC (37.3 per 1000) and CD (10.9 per 1000).\(^6\) A second population study examined the rate of hospitalizations of IBD patients in the US and discovered a similar incidence of CDI, with a rate of 2.8% in UC and 1% in CD.\(^19\) Compared to patients with CD and CDI, those with UC and CDI also had higher rates of surgery (10.4% vs. 8%), and higher mortality rates (5% vs. 3%).\(^20\) Two recent meta-analyses confirm higher rates of both colectomy and mortality in IBD patients with CDI with a more significant effect in UC.\(^21,22\) Although the reason for the increase in incidence of CDI and disease severity among those with UC as compared to CD remains unclear, it is hypothesized that colonic involvement, seen more frequently in patients with UC, may be an attributable risk factor.\(^10\) Interestingly, there was a geographical variation of CDI, with more hospitalizations and higher mortality rates seen in the Northeast region of the US as compared to the Southwest region.\(^23\) The prevalence of asymptomatic and community acquired CDI among the IBD population is also on the rise. Clayton et al. compared 122 individuals with IBD to 99 individuals without IBD and discovered that 8.2% of the IBD population is colonized with *C. difficile*, as compared to 1% of the general population.\(^24\)

CDI appears to have a more aggressive disease course in IBD patients. Ananthakrishnan et al. examined 124,570 hospitalizations among those with CDI and IBD, CDI alone and IBD alone. Patients with IBD and CDI had greater mortality (4.2%) than those with CDI alone (3.7%) or IBD alone (0.5%).\(^20\) Furthermore, the length of hospital stay was longer in the those with CDI and IBD (7 days) as compared to CDI alone (5 days) and IBD alone (4 days).\(^20\) Those with IBD are also more likely to suffer from CDI recurrence, with rates as high as 40% as compared to only 20% of those without IBD.\(^25\) Up to 35% of UC patients had a colectomy one year after diagnosis of CDI, as compared to 9.9% in those without IBD.\(^26\)

**Pathogenesis**

*C. difficile* can be transmitted via fecal-oral route by ingestion of spores. It is easily spread, as it can persist on fomites for several months. Both toxin and non-toxin strains exist though only the toxic strains are associated with disease.\(^27\) Most *C. difficile* strains produce toxin A and toxin B, which are products of *tcdA* and *tcdB* genes. Strains producing one or both toxins are able to cause disease, while strains producing both toxins...
are the most virulent.17 Toxin A, an enterotoxin, binds to intestinal epithelial cells, subsequently damaging intestinal villous tips and the tight junctions between the epithelial cells.28 Toxin B, a cytotoxin, plays a role in promoting neutrophil chemotaxis, and the activation of the cytokine cascade, including tumor necrosis factor (TNF), interleukin (IL)-6, IL-1β, IL-10, and leukotrienes B4 and interferon-γ. This creates a pro-inflammatory state in the mucosa of the intestine, leading to diarrhea, ulceration and the formation of pseudomembranes.29

The natural gut microbiota plays a major role in the defense against CDI, as it stimulates the mucosal immune system and aids in the transformation of secondary bile acids known to inhibit C. difficile germination.30 Distinct changes within the intestinal microbiome have been associated with CDI, including increases in the relative abundance of Proteobacteriacae and Verrucomicrobiota with corresponding decreases in Enterococcaceae, Lactobacillaceae, Prevotellaceae and Spirochaetaceae.31 A decrease in endogenous gut diversity can, therefore, weaken barrier defenses and predispose to CDI. Although the etiology of IBD is unknown, it is theorized that environmental factors and genetics trigger an immune response against the natural bowel flora.32 Subsequently, this leads to chronic inflammation of the intestinal mucosa and a decrease in microbiota diversity.33 It is well known that the ileum plays a major role in the active reabsorption of bile acids, which has a role in inhibiting C. difficile germination. In patients whose terminal ileum is affected by Crohn’s disease, the chronic inflammation can result in the destruction of the sodium/bile acid co-transporting polypeptides located on the ileal enterocytes, which subsequently results in malabsorption of bile acids, and may predispose to CDI.27,34 Genetics may also play a role. Polymorphisms in the IL-4 receptor gene and TNF receptor superfamily member 14 can be associated with IBD and may also increase susceptibility to CDI.35,36 These factors may explain the increased risk of CDI in those with IBD.

**Presentation**

Clinically, *C. difficile* has a wide range of expression, from asymptomatic carrier to toxic megacolon and colonic perforation. Typical diarrhea, nausea, vomiting, abdominal pain, fever and leukocytosis characterize CDI. CDI can mimic IBD flares often making it difficult for physicians to distinguish the two, and thus it is always recommended that all patients with IBD who present with a flare be tested for CDI. CDI might present as bloody diarrhea in IBD patients, which may not be commonly seen in the general population, affected by *C. difficile*. Post-operative IBD patients may be at higher risk of developing CDI than those without a surgical history. The risk can be seen as early as the first 90 days after surgery but can also occur years later.37,38 CDI may manifest as an increase in ileostomy output, and may present as pouchitis in those with an ileal pouch.39 CDI enteritis, a relatively rare entity, occurs almost exclusively in post-operative patients. Roughly half of cases occur in IBD patients and is associated with a high mortality rate.40 Thus the absence of a colon should not preclude the evaluation for CDI. Antibiotics prior to surgery have been shown to increase the risk of CDI.41 Furthermore, it is thought that those who develop CDI immediately post-operative may have had undiagnosed CDI of the colon prior to surgery that subsequently migrates to the small bowel. It has also been shown that the flora of the small bowel mimics colonic flora after colectomy increasing the risk of CDI.38

Endoscopically there exists a key difference between those with CDI and concomitant IBD and those with CDI alone. While pseudomembranes can be seen in up to 60% of those with CDI in the general population, pseudomembranes may not be as common in those with IBD. In a retrospective multi-center study performed in 20 centers in Europe and Israel by Ben-Horin et al, 93 IBD patients with a diagnosis of CDI underwent lower endoscopy. Endoscopic pseudomembranes were seen in only 13% of patients. In those patients who were found to have pseudomembranes, fever was also commonly present.42 In another retrospective study of 24 patients with IBD and CDI, pseudomembranes were not seen endoscopically or histologically in any of the patients.43 It is theorized that in IBD the colon is chronically damaged and cannot mount an adequate local inflammatory response to form pseudomembranes. Another hypothesis is that immunomodulators themselves affect the inflammatory cascade in a way that leads to an absence of pseudomembranes.29,44

**RISK FACTORS**

Traditionally, antibiotic use, in particular clindamycin, fluoroquinolones and broad-spectrum cephalosporin, is considered to be the most common risk factor for CDI. The loss of microbial diversity from antibiotic
use creates an optimal environment that predisposes patients to CDI. In the general population CDI is the etiology in up to 55% of cases of antibiotic associated colitis.44,45 Other risk factors for CDI include older age, residence in long term care facilities, hospitalization, immunosuppression, chronic kidney disease, gastric acid suppression through proton pump inhibitor use, surgery of the gastrointestinal tract and malignancy.46

IBD patients constitute a unique risk group as they tend to be young individuals with a history of outpatient-acquired infections and overall less antibiotic exposure compared to the general population.44 Population studies have demonstrated that up to 40% of CDI in IBD had no prior antibiotic exposure and that 76% of cases were diagnosed in the outpatient setting.43,47 Multiple studies have also found that colonic involvement is an important risk factor for CDI in IBD.43,44 In one single center study, Issa et al. found that up to 91% of patients with IBD who were diagnosed with CDI had colonic involvement.48 A second population study demonstrated that those who had IBD with colonic involvement had a 3.5 times higher incidence of CDI compared to those whose inflammatory disease only affected the small bowel.6

CDI is also associated with high rates of colectomy and mortality amongst patients with IBD.21,22 Studies have shown an incidence of CDI ranging from 10% to 18.3% in patients who underwent an ileal pouch-anal anastomosis.41,48 Ananthakrishnan et al. analyzed the occurrence of colectomy and/or death within 180 days of CDI in a retrospective multi-institution database of IBD patients. Approximately 20 percent of patients met this endpoint at a median of 31 days and predictors of severe outcomes included albumin <3 g/dL (HR 2.97), hemoglobin <9 mg/dL (HR 2.51), age >65 (HR 2.14) and serum creatinine >1.5 g/dL.59

In comparison to the general population, use of proton pump inhibitor medications has been reported to be lower in IBD patients with CDI than in non-IBD patients with CDI.50 Furthermore, Ananthakrishnan et al. found that 25(OH)-Vitamin D levels differed significantly amongst IBD patients with and without CDI (20.4 vs. 27.1, respectively) and levels below 20 ng/mL were associated with an odds ratio of 2.27 for CDI.51

The use of immunomodulators is also an important risk factor that should be well recognized. Issa et al. reported that 78% of patients with IBD and CDI were on immunosuppressive medication, including azathioprine, 6-mercaptopurine, methotrexate and infliximab.43 Schneeweiss et al. analyzed 10,662 IBD patients and discovered that those on steroids were three times more likely to acquire CDI as compared to those on other immunosuppressant agents.52 In this study the use of infliximab did not increase risk of CDI, which is in contrast to the RECIDIVISM study, which discovered that infliximab, and not adalimumab, was associated with increased recurrence of CDI compared to adalimumab.50

Lastly, analysis of the Food And Drug Administration Adverse Events Reporting System showed an increased incidence of CDI amongst patients receiving therapy with vedolizumab, but not with anti-TNF biologics.53 Based on these studies, steroids appeared to increase the risk of CDI, but there have been inconsistent findings regarding the risk of biologics.

Diagnosis

Diagnosis of CDI in IBD patients is the same as the diagnosis in the general population. Multiple diagnostic modalities are available, including cell cytotoxicity assays, enzyme immunoassay (EIA) for toxin (tcdA and tcdB), culture, glutamate dehydrogenase (GDH) detection, nucleic acid amplification tests (NAAT) and multi-step algorithms. Regardless of the modality chosen, testing should only be performed on diarrheal stool as testing on formed stool can decrease the specificity of diagnosis confusing a carrier with an active infection.54 The gold standard for the diagnosis of CDI is stool culture for toxin which requires growing C. difficile and an additional step to detect the presence of toxin. This test is time and labor intensive, taking up to 48 hours for results.55 Thus, rapid testing is commonly preferred. One such test is GDH detection via EIA, however, GDH is present in both toxigenic and non-toxigenic strains, therefore, testing for GDH requires an additional modality that detects toxin. Due to the complexity and time sensitivity of CDI diagnosis, many have suggested multistep algorithms for rapid diagnosis.25,54,55 Multistep algorithms involve a two-step process, initially using a highly sensitive test to screen for CDI that is reflexively followed by a highly specific test to confirm the diagnosis. Detection of GDH has a high negative predictive value and is commonly used as the first step in many proposed multistep algorithms. One systematic review found that diagnosis with multistep algorithms using PCR for toxin or single step PCR on liquid stools may have the best outcome.
(multistep: sensitivity 0.68-1.00 and specificity 0.92-1.00; single step: sensitivity 0.86-0.92 and specificity 0.94-0.97). Thus, EIA for GDH and toxin or PCR for \textit{tcdB} gene seem to be the most commonly applied tests in clinical practice.

The American College of Gastroenterology guidelines recommend screening for CDI in IBD patients who are hospitalized for a flare and IBD patients who develop diarrhea when disease activity was previously in remission or have risk factors for CDI.\textsuperscript{57} Colonoscopy is not commonly used in the diagnosis of CDI in the general population, as there are other less invasive modalities available. However, in the IBD population, colonoscopy may be used more frequently as presentation of CDI and IBD can be similar but its value in differentiating the two may be limited. Nevertheless it is important to remember that the typical findings of pseudomembranes are not commonly found in IBD patients and the histologic findings may be difficult to differentiate from IBD.\textsuperscript{41} Computed tomography scans may aid in the diagnosis of CDI if typical features of CDI are present (i.e. nodular hastral thickening or the accordion pattern), however, this test is also limited by a lack of specificity.\textsuperscript{58}

\section*{Treatment}

Treatment of CDI is based on the severity of CDI, defined as mild to moderate (leukocytosis with white blood cell count <15,000 cells/μL and serum creatinine level <1.5 times the premorbid level), severe (leukocytosis with a white blood cell count of ≥15,000 cells/μL or a serum creatinine level ≥1.5 times the premorbid level, serum albumin <3 g/dL) or severe complicated (hypotension or shock, ileus, megacolon).\textsuperscript{54,57} In addition, whether the diagnosis is a primary event or a recurrence also determines the course of treatment.

There are three antibiotics that are recommended in the treatment of CDI among the general population, including metronidazole, vancomycin and fidaxomicin. Metronidazole is the drug of choice for mild to moderate CDI, whereas, vancomycin is preferred in severe CDI.\textsuperscript{54} Previous studies have shown that in severe and complicated CDI metronidazole has a higher rate of treatment failures.\textsuperscript{56} In addition, metronidazole may be inferior to vancomycin despite the severity of disease suggesting vancomycin should be the first choice in the treatment of CDI.\textsuperscript{59,60}

Fidaxomicin is the most recently approved antibiotic for the treatment of primary and first recurrence CDI. It was introduced in 2011 when Louie et al. showed that the rates of cure with fidaxomicin were non-inferior to the rates of cure with vancomycin.\textsuperscript{61} In addition, fidaxomicin was associated with a significantly lower rate of recurrent CDI.\textsuperscript{62} Unfortunately, the use of fidaxomicin is limited by its high cost.\textsuperscript{63}

Fecal microbiota transplantation (FMT) has a role in CDI. FMT changes the bacterial composition of the gut microbiota, and has been associated with resolution of CDI symptoms.\textsuperscript{64} FMT is 70-91\% effective in achieving cure after initial treatment and 89-98\% effective in overall cure.\textsuperscript{65,66} Systematic reviews have found an 89.7\%-92\% cure rate of recurrent CDI after FMT.\textsuperscript{68,69} There are no randomized controlled trials assessing the role of FMT in primary non-recurrent CDI, however, Lagier et al. conducted an open label, nonrandomized, prospective study assessing early (within one week of infection) FMT via nasogastric infusion with fresh stool in primary CDI that showed a significant reduction in mortality.\textsuperscript{70} Unfortunately, the route (oral vs. endoscopic), stool preparation (fresh vs. frozen), amount of stool infusate and donor characteristics have not been standardized.

Monoclonal antibodies to \textit{C. difficile} toxin are now available to decrease CDI recurrence when part of the initial treatment algorithm.\textsuperscript{71} There are two monoclonal antibodies that have been evaluated in the prevention of recurrent CDI, actoxumab and bezlotoxumab, which bind and neutralize \textit{C. difficile} toxins A and B, respectively. Wilcox et al. conducted two multicenter randomized, double blind, placebo-controlled trials (MODIFY I and MODIFY II) with participants with either primary CDI or recurrent CDI who were treated with standard of care antibiotics (vancomycin, metronidazole or fidaxomicin) for 10-14 days. They found that the rate of recurrent CDI was significantly lower with bezlotoxumab alone than with placebo (MODIFY I: 17\% vs. 28\%; 95\% CI -15.9 to -4.3; P<0.001; MODIFY II: 16\% vs. 26\%; 95\% CI -15.5 to -4.3; P<0.001) and significantly lower with actoxumab plus bezlotoxumab than with placebo (MODIFY I: 16\% vs. 28\%; 95\% CI -17.4 to -5.9; P<0.001; MODIFY II: 15\% vs. 26\%; 95\% CI -16.4 to -5.1; P<0.001).\textsuperscript{72} The original MODIFY I trial included an actoxumab alone arm, however, this arm was discontinued after planned interim analysis did not show efficacy. The rates of recurrent infection were lower in both groups that received bezlotoxumab compared to the placebo group. Approximately, 20\% of participants included...
in the study were immunocompromised, however, supplementary material do not distinguish the defining characteristics of those subjects. Bezlotoxumab’s role in the treatment of IBD patients with CDI is undefined.

Management of CDI in IBD

The management of CDI in IBD patients is difficult as the symptoms cannot be attributed to either IBD flare or CDI alone. Many patients with IBD are immunocompromised often due to treatment with immunomodulators or biologics making the choice of treatment difficult. In a non-IBD population hospitalized with CDI, use of corticosteroids within 2 weeks of diagnosis has been associated with a two-fold increase in mortality.73 De-escalation of corticosteroid dose may lessen the severity of an active CDI.43 Patients with IBD and a concomitant CDI treated with immunomodulators and antibiotics had poorer outcomes than those treated with antibiotics alone. This was based on 155 patients (antibiotics: n = 51 vs. antibiotics and immunomodulators: n =104).74 In contrast, Lukin et al. recently performed a multi-center retrospective cohort study of 157 patients with IBD and CDI that assessed immunosuppressive medications on the clinical outcome in this patient population. They found a marked increase in serious outcomes (i.e. death, sepsis, colectomy) among patients who did not have an escalation of IBD therapy within 90 days of CDI suggesting a subpopulation of IBD with CDI where CDI is a marker of disease severity.75 This concept is supported by the data from Ananthakrishnan et al, but goes further in suggesting that a specific subpopulation of patients with CDI and IBD could be harmed if IBD therapy is not escalated.10

No prospective studies have been performed to assess the antibiotic preference of CDI in IBD patients, however, as CDI in IBD is high risk and a complicated disease, it is reasonable to consider vancomycin as first line treatment in these patients.59 This group may also be ideal to benefit from toxin B antibody during initial treatment, though no studies in IBD patients have yet been performed.

There is a growing consensus that FMT may be used in the treatment of CDI in UC patients. A systematic review of 17 articles that assessed FMT in IBD found 15 IBD patients (8 UC and 7 CD) with CDI who were treated with FMT. There was outcome data for 12/15 with resolution of CDI when treated with FMT based on negative stool sample enterotoxin. However, only 11/12 patients had reduction or complete resolution of diarrhea.76 Another multicenter retrospective series that assessed FMT for CDI treatment in immunocompromised patients included 36 patients with IBD. In the IBD patients, they found resolution of CDI in 86% of patients after a single FMT and an overall cure rate of 94%.66 In a prospective study examining FMT for the treatment of refractory CDI by Hamilton et al., 14 of 43 study patients were reported to have UC.72 While no subgroup analysis is provided, all UC patients were reported to have improved from CDI after FMT. A more recent prospective study reported cure rates of 79% after first FMT and 90% overall in IBD patients undergoing FMT for CDI.78 In this study, treatment failure was associated with hypoalbuminemia. Additionally, the durability of FMT within IBD patients appears to be less than in the general population. In a small pediatric study in recurrent CDI, analysis of the fecal microbiome in patients both with and without IBD resembled that of the donor immediately following FMT but the microbiome in patients with IBD returned to a signature resembling that before FMT after 6 months.79 Lastly, the possibility of FMT-related adverse effects, including exacerbation of IBD, remains uncertain.66,80 Thus, there may be benefit in treatment of CDI in IBD patients with FMT; however, larger studies need to be performed to assess FMTs efficacy and potential adverse effects in IBD patients with CDI.

In 2013, the American College of Gastroenterology put forth guidelines for the management of *C. difficile* infection, which include recommendations for patients with IBD.57 These guidelines emphasize that CDI must be suspected in all IBD patients hospitalized for or presenting for outpatient evaluation of a presumed disease flare, including patients with ileal pouch following total proctocolectomy. While there is low-quality evidence currently available to guide IBD treatment at the time of CDI, these guidelines advocate for the simultaneous empiric treatment of CDI and IBD while awaiting the results of diagnostic testing. Maintenance of ongoing immunosuppressive therapy is recommended during active CDI, but escalation of
therapy is advised only after appropriate treatment of the infection for 72 hours. Further, high quality prospective studies are needed to inform future treatment guidelines.

CONCLUSION

CDI is an increasing health concern due to the virulence of B1/NAP1/027 strain with prevalence increasing in both the hospital and community setting. CDI is particularly important in IBD patients as it complicates the disease course and increases morbidity and mortality. CDI in IBD can be difficult to diagnose as it can mimic or complicate IBD flares and does not classically present in the same manner as the general population, such as increased asymptomatic carriage and community acquired CDI and a decrease in frequency of pseudomembranes in the IBD population. All patients with IBD who have an acute flare of their disease should be tested for CDI. There are multiple antibiotics available in the treatment of CDI; however, oral vancomycin may be the preferred agent in IBD patients. FMT and monoclonal antibodies to toxin B are two newly proposed modalities to aid in the treatment of CDI, however, their role in CDI and IBD is currently unclear. Immunosuppression in IBD patients with CDI can also be difficult to manage, however, a recent study has shown that there may be a benefit to corticosteroids and biologics after antibiotic treatment for CDI. There is a developing body of information regarding CDI in IBD management, however, further studies are still required to establish a standard of care and management.

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